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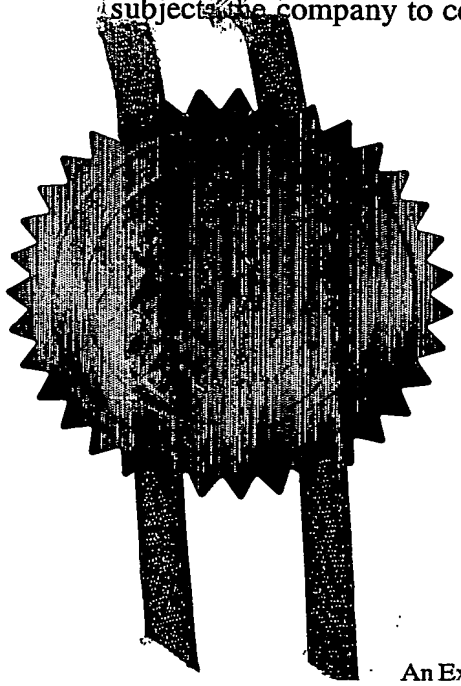

Signed P. Mahoney

Dated 16 October 2003

Patents Form 1/77

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17SEP02 E748785-1 D100324
P01/7700 0.00-0221513.5

THE PATENT OFFICE
17 SEP 2002
NEWPORT

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference PRA/PDJ/1

2. Patent application number *(The Patent Office will fill in this part)* 0221513.5 17 SEP 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GENERICS [UK] Ltd.,
Albany Gate, Dakes Lane,
Potters Bar,
Herts, EN6 1AG

Patents ADP number *(if you know it)* 8118747001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

Novel Compounds and Processes.

5. Name of your agent *(if you have one)*

PRIVATE APPLICANT

DR PAUL JENKINS
Address as above.

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Patents ADP number *(if you know it)* 8465866001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*
N/A		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*
N/A	

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or

b) there is an inventor who is not named as an applicant, or

c) any named applicant is a corporate body.
See note (d))

YES

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Continuation sheets of this form	0
Description	8
Claim(s)	1
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority documents	—
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	—
Request for preliminary examination and search *(Patents Form 9/77)*	—
Request for substantive examination *(Patents Form 10/77)*	—
Any other documents *(please specify)*	—

11. I/We request the grant of a patent on the basis of this application.

Signature P. D. JENKINS Date 13/9/02

12. Name and daytime telephone number of person to contact in the United Kingdom DR PAUL JENKINS 01707 853249

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Notes

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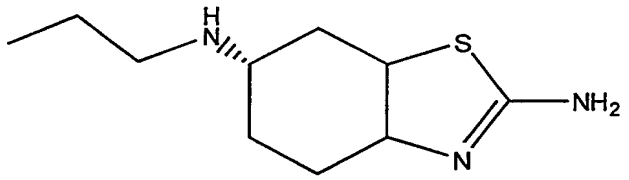
Novel Compounds and Processes

The present invention relates to novel cyclohexanes and cyclohexanones and to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles.

Certain 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are known to have dopamine D-2 activity and are therefore potentially useful as pharmaceuticals for the treatment of psychiatric disorders such as schizophrenia and Alzheimer's Disease. One such compound, the dihydrochloride salt of (S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole **I** (pramipexole) is marketed as a pharmaceutical for the treatment of Parkinson's Disease.



I

Processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are disclosed in patents US 4843086, US 4886812 and patent applications WO 02/22590 A1 and WO 02/22591 A1. A procedure to these types of compound is also disclosed by C S Schneider & J Mierau in J Med Chem, **1987**, *30*, 494-498.

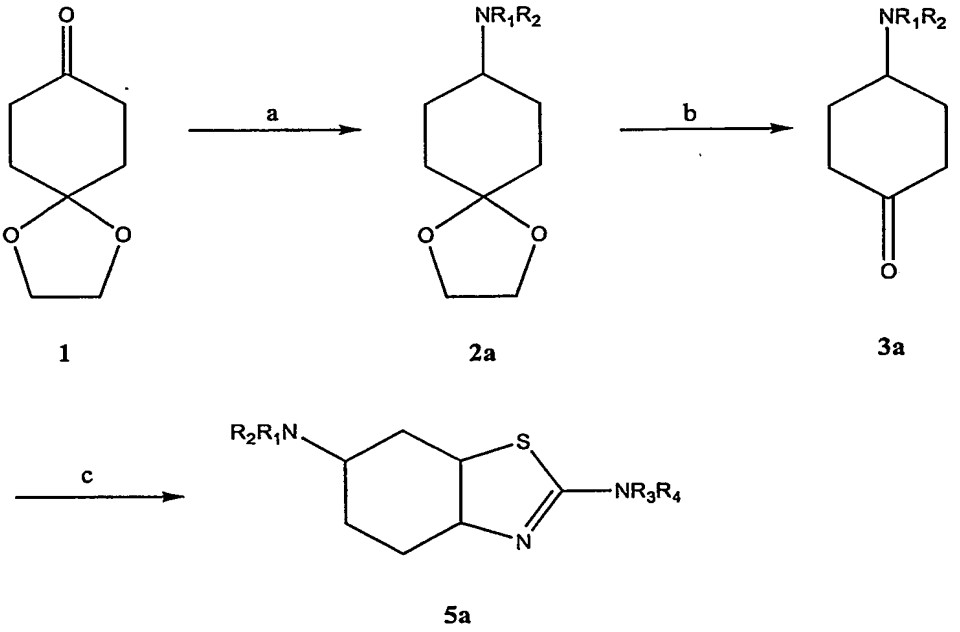
However, known processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are not satisfactory, particularly for industrial scale manufacture, as they have been found to be low yielding and involve the use of hazardous and difficult to handle reagents such as bromine, hydrazine and potassium chromate.

The inventors have found that processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles are greatly improved by the

process outlined in **Scheme One**, wherein R_1 and R_2 can be any atom or group (or together form a ring) and R_3 is hydrogen and R_4 can be any atom or group. R_1, R_2 and R_4 are preferably a hydrogen group, or an alkyl, aryl or heteroaryl group.

The process outlined in **Scheme One** is short and utilises a readily available starting material, cyclohexandione monoethyleneketal **1** and does not require any hazardous chemical reagents. Each step of the process is high yielding and affords products of very high purity.

Therefore a first aspect of the current invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a** by the process specified in **Scheme One.**



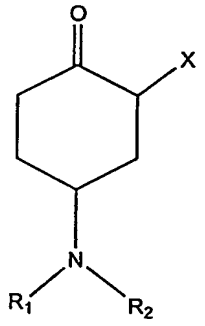
1 **2a** **3a**

5a

a: Reductive amination, R_1R_2NH
b: Deprotection
c: (i) Iodine, $H_2N(C{=}S)NR_3R_4$ (ii) ^-OH

Scheme One

It has been disclosed in the prior art documents, WO 02/22590 and WO 02/22591, that in practice compounds of formula **5a** , comprising a primary amino or a secondary alkylamino group cannot be prepared directly from the corresponding ketones **3a**. The process shown in **Scheme One** illustrates that the process of the current invention does indeed allow a compound **5a** to be prepared from ketone **3a** directly without the requirement of preparing and isolating a α-haloketone of formula **4** (where group X is a halide group such as chloride or bromide) and/or the requirement of a protecting group on the nitrogen atom of the amine substituent of the cyclohexanone ring.



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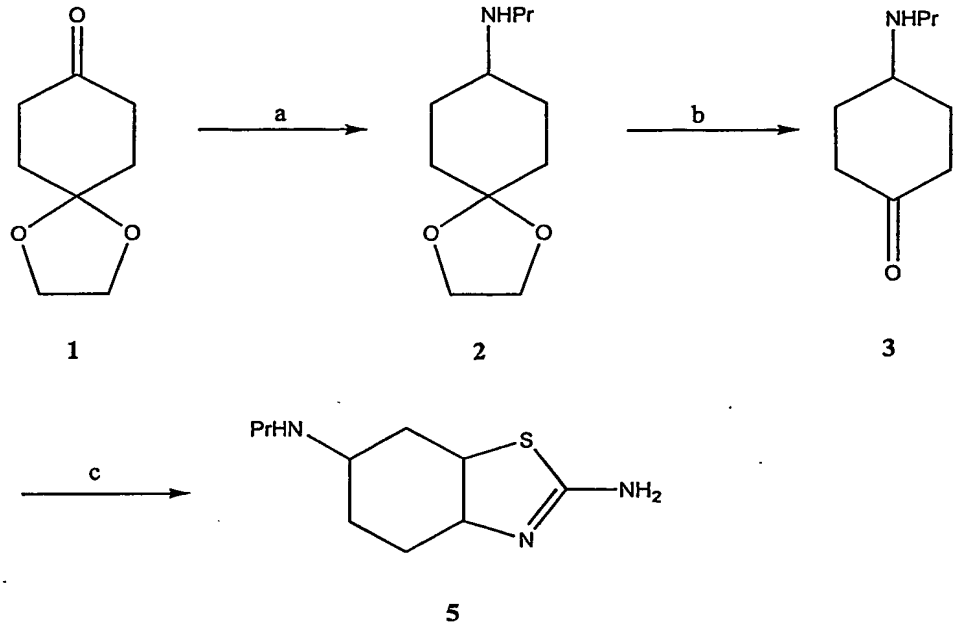
A preferred embodiment of the first aspect of the invention is a process for the preparation of 2-amino-4,5,6,7-tetrahydro-6-(propylamino)-benzothiazole **5** as outlined in **Scheme Two**.

The process outlined in **Scheme Two** can readily be adapted to afford pramipexole **I** and/or it salts (*eg* by resolution of compound **5**).

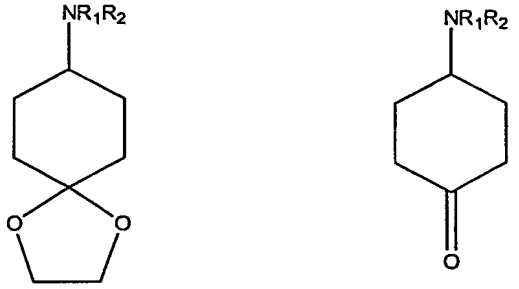
A further aspect of the invention is therefore pramipexole **I** and/or it salts when prepared by a process according to the current invention.



a: n -Propylamine, $NaCNBH_3$, MeOH/HCl
b: aq HCl/THF
c: (i) Iodine, thiourea, ethanol, reflux (ii) aq NaOH

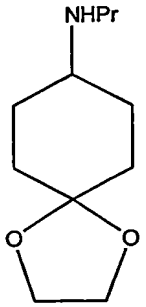
Scheme Two

Further aspects of the invention include novel compounds of the type **2a** and **3a**, wherein R_1 and R_2 are as defined above, which are useful intermediates in the synthesis of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles **5a**.



2a **3a**

Preferred embodiments of these aspects are compounds **2** and **3**.



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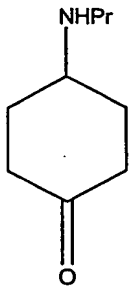

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The process outlined in **Scheme Two** is an example of a procedure comprising the process of the current invention and detailed procedures for this process is found in the experimental section. Compounds of the current invention are also exemplified in **Scheme Two** and in the experimental section.

EXPERIMENTAL PROCEDURE

4-n-propylaminocyclohexanone-ethyleneketal (2)

A mixture of n-propyl amine (162mL, 1.474moles) in methanol (500mL) was chilled to 0-5°C. To this solution was added methanolic hydrochloric acid (155mL, 44.47%) dropwise over a period of 30mins to achieve a pH of 6 to 7. Cyclohexandione monoethyleneketal (100g, 0.641moles) was charged at 5°C and the reaction was stirred for 15mins. Sodium cyanoborohydride (60g, 0.952moles) was added in15mins at 5°C. The pH increased to about 8 and methanolic hydrochloric acid (15mL, 44.47%) was added to bring the pH to 6-7. The reaction was allowed to come to 24-26°C. Stirring was continued for 2h. Methanol was distilled off (450mL). Sodium carbonate (95g, 0.896moles) was dissolved in water 850mL and charged to the reaction mass at ambient temperature in one shot. The reaction mass was extracted with dichloromethane (2500mL). The dichloromethane layers were combined and

dried over sodium sulfate (8.5g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product was light yellow viscous oil. The weight of the product obtained was 135g (105.8%). GC purity 97.74%.

^{1}H NMR (δ ppm): 0.9-1.0, (t, 3H, CH_3 of nPr); 1.5-1.7 (m, 7H, **CH_2CH_3** of nPr, 5H of cyclohexyl ring); 1.75-1.85, (m, 2H, 2H of cyclohexyl ring); 1.95-2.05, (m,1H, 1H of cyclohexyl ring); 2.75, (t, 2H, **$CH_2CH_2CH_3$** of nPr); 3.75-3.85, (m, 1H, NH**CH**); 3.9 (s, 2H, CH2 of ethylene ketal) and 4.0, (s, 2H, CH2 of ethylene ketal).

^{13}C NMR (δ ppm): 11.7, (CH_3 of nPr); 21.8, (**CH_2CH_3** of nPr); 28.5, (2*C, C-3 and C-5); 33.1, (2*C, C-2 and C-6); 48.3, (1C, **C**$H_2CH_2CH_3$ of nPr); 55.8, (C-4); 64.5, (C of ethylene ketal); 64.6, (C of ethylene ketal); 108.1, (C-1).

4-n-propylaminocyclohexanone (3)

4-N-propylamino-cyclohexanone-ethyleneketal **2** (134g, 0.673moles) was taken in tetrahydrofuran (268mL) and cooled to 4-6°C. Concentrated hydrochloric acid (178mL, 2.01moles) was diluted with water (2144mL) and the mixture was cooled to 4°C. This diluted hydrochloric acid was added to the reaction mixture at 4-6°C in 15mins. The reaction was allowed to come to 24-26°C and stirring was continued for 24h. The reaction mass (2750mL) was concentrated to 1800mL at 50°C and 35mbar pressure. Sodium carbonate (148g, 1.4moles) was added to achieve pH 10. The reaction mixture was extracted with dichloromethane (3670mL). The dichloromethane layers were combined and dried over sodium sulfate (20g). The dichloromethane layer was concentrated to dryness at 40°C and 15mbar pressure. The product was yellow viscous oil. The weight of the product obtained was 52.5g (52.84%). GC purity 86.07%.

Spectral / characterization data :

^{1}H NMR (δ ppm): 0.9-1.0, (t, 3H, CH_3 of nPr); (m, **CH_2CH_3** of nPr); 1.6-1.75, (m, 2H, 2H of cyclohexyl ring); 2.05-2.15, (m,2H, 2H of cyclohexyl ring); 2.2-2.3, (m,2H, 2H of cyclohexyl ring); 2.4-2.55, (m,2H, 2H of cyclohexyl ring); 2.55-2.65, (t, 2H, $CH_2CH_2CH_3$ of nPr); 2.9-3.0, (m, 1H, NHCH)

^{13}C NMR (δ ppm): 12.3, (CH_3 of nPr); 24.0, (CH_2CH_3 of nPr); 32.6, (2C, C-3 and C-5); 39.1, (2*C, C-2 and C-6); 50.0, ($CH_2CH_2CH_3$ of nPr); 54.4, (C-4); 211.9, (C-1).

2-amino-6-n-propylamino-5,6,7,8-tetrahydrobenzthiazole (5)

4-n-propylamino-cyclohexanone **3** (5g, 32.26mmol) was charged in absolute ethanol (50mL) at 24-26°C. Iodine (8.5g, 33.5mmol) was added to it under stirring followed by thiourea (5g, 65.7mmols) at 24-26°C. The reaction mass was refluxed for 32h. Heating was stopped and the reaction mass was allowed to cool to 24-26°C. It was maintained at that temperature for 20h. 2-amino-6-n-propylamino-cyclohexanone dihydroiodide crystallized out of the solution. Ethanol (30mL) was distilled out on the rotavapor at 50°C and 100mbar. Acetone (50mL) was added and the solid was filtered. The solid was dried at 40°C and 15mbar. The weight of the product obtained was 8.5g (56%) HPLC purity 94.97%.

Spectral / characterization data :

^{1}H NMR (δ ppm): 0.9-1.0, (t, 3H, CH_3 of nPr) 1.6-1.8 (m, 2H, **CH_2**CH_3 of nPr); 2.0, (m, 1H, H-7a); 2.35, (m,1H, H-7b); 2.7, (m,3H, H-5a,H-8a, H-8b); 3.1, (m,3H, H-5b, $CH_2CH_2CH_3$ of nPr); 3.7, (m, 1H, NHCH)

^{13}C NMR (δ ppm): 12.0, (CH_3 of nPr); 21.0, (CH_2CH_3 of nPr); 22.2, (C-7); 25.5 and 26.8, (2C, C-5, C-8); 48.7, ($CH_2CH_2CH_3$ of nPr); 54.7, (C-6); 113.0, (C-4), 134, (C-9), 171.2, (C-2)

Mass Spec: M^+ 211 (expected 211)

The 2-amino-6-n-propylamino-cyclohexanone dihydroiodide salt formed above (50g, 107.1mmols) was dissolved in water (200mL). The solution was cooled to 4°C and solid sodium hydroxide (50g, 1.25moles) was added in 15mins. The reaction was stirred for 1h at 24-26°C and the solid that precipitated out was filtered and dried at 40°C and 15mbar. The weight of the product obtained was 17.07g (75.5%) HPLC purity 99.88%.

^{1}H NMR (δ ppm): 0.9-1.0, (t, 3H, CH_3 of nPr); 1.5-1.6 (m, **CH_2**CH_3 of nPr); 2.1, (m, 1H, H-7a); 2.3, (m,1H, H-7b); 2.5-2.6, (m,5H, H-5a, H-5b, H-8a, H-8b, $CHCH_2CH_3$ of nPr); 2.9, (m,2H, H-6, $CHCH_2CH_3$ of nPr)

^{13}C NMR (δ ppm): 12.0, (CH_3 of nPr); 24.6, (CH_2CH_3 of nPr); 26.6, (C-7); 30.7 and 30.9, (2C, C-5, C-8); 50.7, ($CH_2CH_2CH_3$ of nPr); 56.2, (C-6); 116.0, (C-4), 145, (C-9), 170.4, (C-2)

Mass Spec: M^+ 211 (expected 211)

Claims

1. A process according to Scheme One wherein wherein R_1 and R_2 can be any atom or group (or together form a ring) and R_3 is hydrogen and R_4 can be any atom or group.
2. A process according to Scheme Two.
3. Compounds of formula 2a.
4. Compounds of formula 2.
5. Compounds of formula 3a.
6. Compounds of formula 3.
7. Pramipexole I and/or it salts when prepared by a process according to claims 1 or 2.

Abstract

The present invention relates to novel cyclohexanes and cyclohexanones and to processes for the preparation of 2-amino-4,5,6,7-tetrahydro-6-aminobenzothiazoles.